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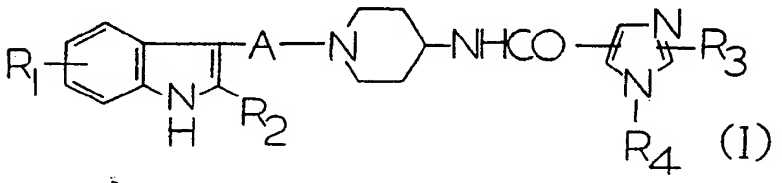
(56) Documents cited
None

(58) Field of search
C2C

(54) Indole derivatives

(57) Indole derivatives of formula I



(I)

in which R_1 is hydrogen, lower alkyl, halogen, lower alkoxy or hydroxy,
R_2, R_3 and R_4 independently represent hydrogen or lower alkyl,
A represents an alkylene, oxoalkylene or hydroxyalkylene chain each having 2 to 6 carbon atoms or a pharmaceutically acceptable salt thereof, possess *antihypertensive activity* whilst exhibiting *reduced CNS depressant properties.*

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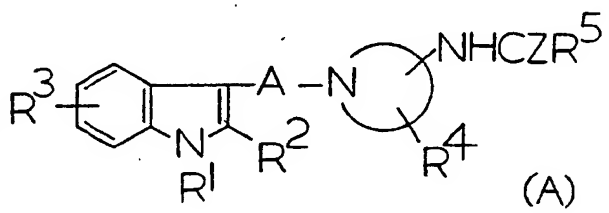
Formulae in the printed specification were reproduced from drawings submitted after the date of filing, in accordance with Rule 20(14) of the Patents Rules 1982.

SPECIFICATION

Indole derivatives

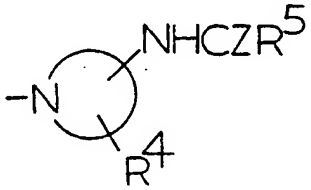
This invention relates to indole derivatives possessing pharmaceutical acitivity, more particularly to indolylpiperidine derivatives, processes for their preparation and pharmaceutical compositions containing them.

In our UK Patent Specification No. 1,218,570 there are described and claimed a class of indole derivatives possessing (inter alia) antihypertensive activity and having the formula:

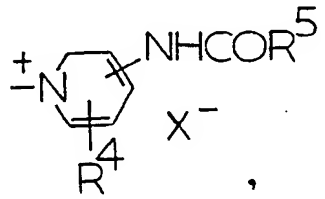


(A)

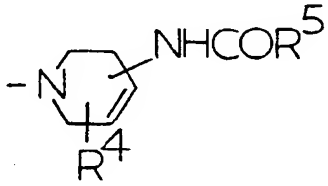
in which formula



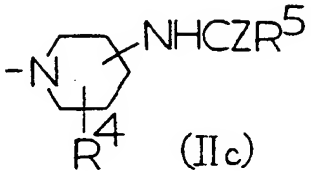
represents a ring system of the general formula



(IIa)



(IIb)



(IIc)

R^1 represents hydrogen, lower alkyl, lower aralkyl or aroyl, R^2 represents hydrogen, lower alkyl or aryl, R^3 represents hydrogen, halogen, lower alkoxy, hydroxy or lower alkyl, R^4 represents hydrogen, halogen or lower alkyl, R^5 represents aryl (including heterocyclic aryl), lower alkoxy, aryloxy, lower aralkyl, lower aralkyloxy or diaryl-lower alkyl, X is an anion, A represents an alkylene or mono- or di-keto alkylene radical containing up to 4 carbon atoms, and Z is an oxo (i.e.=0) group with the proviso that Z in formula II(c) may also represent two hydrogen atoms when A is alkylene and R^5 is aryl.

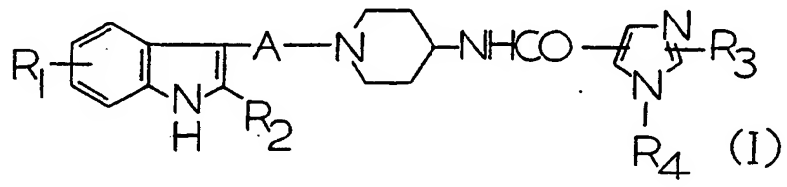
Examples of heterocyclic aryl groups for R^5 were given as 3-indolyl, 2-thienyl and 2-furyl. One of the compounds falling within the scope of formula A is a valuable antihypertensive agent having the generic name indoramin and the chemical name 3-[2-(4-benzamido)-1-piperidyl)-ethyl]-indole.

Indoramin is used for the treatment of elevated blood pressure in patients and is extensively described in the literature, see–for example "Indoramin in the Treatment of hypertension" The Practitioner, October 1983 Vol. 227. As UK Patent Specification No. 1,218,570 acknowledges the compounds of formula A also possess central nervous system activity and in the case of indoramin such activity is manifest as sedation in a proportion of patients. Latest available figures suggest sedation is not serious but is the main side effect occurring in about 18 per cent of patients. It appears to contribute to the withdrawal of only 3.8% of patients which is regarded as very acceptable in the context of antihypertensive treatment. Nevertheless sedation is the dose limiting side effect for indoramin.

We have surprisingly found a class of imidazolyl derivatives falling within the scope of formula A, which compounds possess antihypertensive activity of the same order as indoramin but do not have the same propensity as indoramin to cause depression of the central nervous system.

In particular sedation is less likely to occur

Accordingly this invention provides compounds of formula:



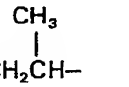
(I)

wherein R_1 is hydrogen, lower alkyl, halogen, lower alkoxy or hydroxy; R_2 represents hydrogen or lower alkyl; A represents an alkylene, oxoalkylene or hydroxyalkylene chain each having 2 to 6 carbon atoms and R_3 and R_4 independently represent hydrogen or lower alkyl, and pharmaceutically acceptable salts thereof.

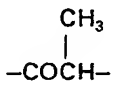
By the term lower as used herein is meant groups having 1 to 6 carbon atoms preferably 1 to 4. Examples of lower alkyl groups for each of R_1, R_2, R_3 and R_4 are methyl, ethyl, n-propyl and isopropyl.

Examples of lower alkoxy groups for R_1 are methoxy, ethoxy, n-propoxy and n-butoxy.

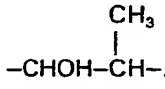
Examples of alkylene chains for A are $-(CH_2)_n-$, $-CO(CH_2)_{n-1}$ and $-CHOH(CH_2)_{n-1}$ in which n is an integer from 2 to 4. Branched chain groups are also included such as



providing such groups contain at least 2 carbon atoms in the main chain linking indole to piperidine. Other examples include



and



Preferred halogen groups for R_1 include chlorine and bromine.

The imidazolyl group is bonded to the –NHCO– group via any of the ring carbon atoms and is preferably imidazol–2–yl or imidazol–4–yl.

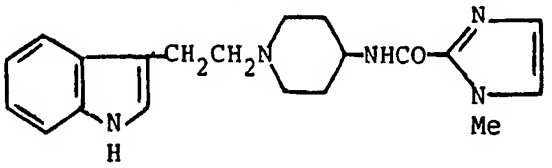
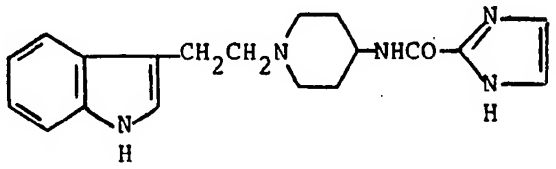
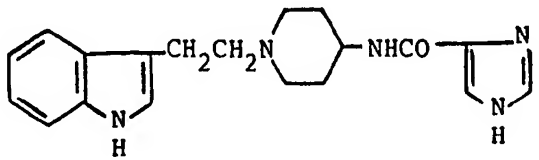
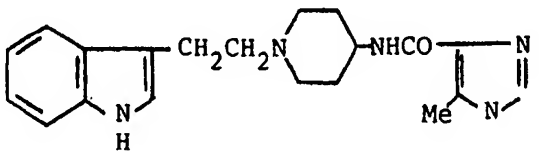
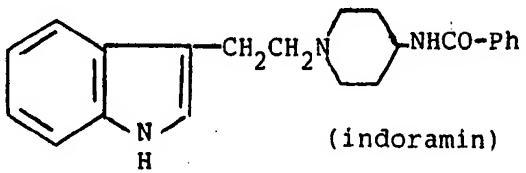
The compounds of formula I possess pharmaceutical activity, in particular antihypertensive and/or hypotensive activity when tested on warm blooded animals and hence are indicated for the treatment of high blood pressure.

The compounds of formula I were tested for antihypertensive activity by the following standard procedure:

The blood pressures of male or female spontaneously hypertensive rats are measured in a 37°C constant temperature housing by means of a tail cuff. Rats with systolic pressures below 155 mmHg are discarded. Groups of rats are dosed orally with the test substance in a suitable vehicle or with vehicle alone. Systolic pressures are recorded before dosing and at selected time points afterwards. Heart rates are derived from caudal artery pulses. Results are analysed statistically by means of 2 way analysis of variance (within group).

In this procedure representative compounds of the invention gave the results shown in the following Table:–

TABLE 1

COMPOUND	DOSE/LEVEL (mmol/kg po)	BLOOD PRESSURE as % of pre-dose level (time t after dosing) t= 2 hrs.	6 hrs.
	0.15	53%	59%
	0.03	70%	84%
	0.15	60%	70%
	0.15	67%	68%
	0.15		57%
 (indoramin)	0.15	62%	66%

The results in Table 1 show that the representative compounds of this invention possess the same order of antihypertensive activity as the commercially available antihypertensive agent indoramin.

The compounds of formula I were also tested for central nervous system activity in mice specifically to determine whether and at what dose levels symptoms associated with sedation were present. The following test procedure was used:

Groups of three female mice (18–25g) are dosed with the test compound. The usual doses tested are 400, 127, 40 and 12.7 mg/kg and both the oral and intraperitoneal routes are used. The drug is routinely suspended in 5% hydroxypropylmethylcellulose (HPMC).

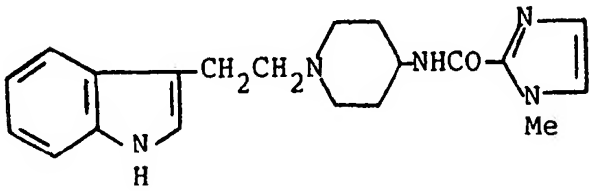
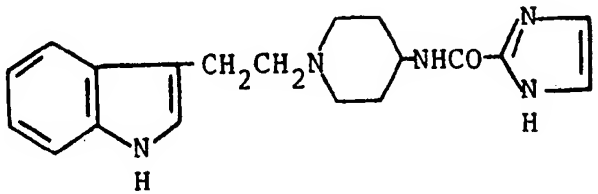
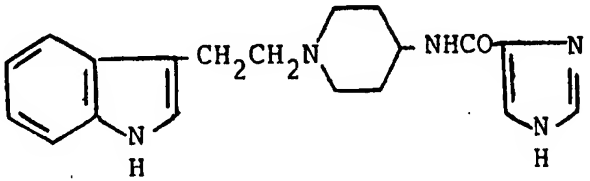
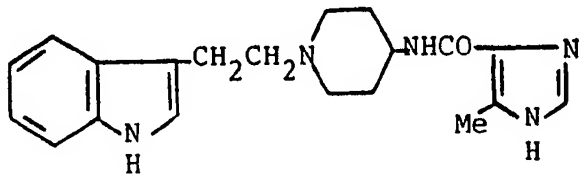
The animals are observed over a two hour period. The activities looked for during the observation period include:–

i) signs of general stimulation (i.e. increased motor activity, tremor, stereotypy)

ii) signs of general depression (i.e. decreased motor activity, sedation, hypothermia.

The following results were obtained for representative compounds of formula I:

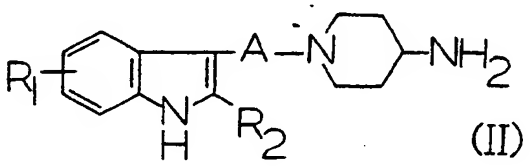
TABLE 2

COMPOUND	Drug level at which following symptoms were first observed (mg/kg)		
	Sedation	Hypothermia	Decreased Motor Activity
	127	40	12.7
	400	>400	40
	>400	>400	>400
	>400	>400	127
indoramin	40	40	4

The results in Table 2 show the compounds of formula I are much weaker CNS depressants than indoramin requiring much higher dose levels to produce the symptoms of sedation, hypothermia and decreased motor activity. Accordingly the compounds of formula I whilst being as potent as indoramin in lowering blood pressure are much more selective in that they do not have the same propensity to cause depression in the CNS.

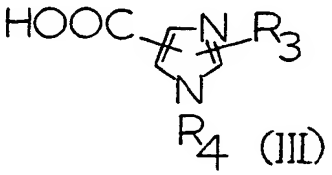
This invention also provides processes for preparing the compounds of formula I. In general these methods correspond to those for preparing the compounds of formula A described in UK Patent Specification Nos. 1,218,570, 1,375,836, 1,399,608, 1,543,619 and 1,542,137 and generally involve building up the molecule in known manner from appropriate starting materials comprising reactive substituent groups.

A first process for preparing compounds of formula I comprises acylating a compound of formula



(II)

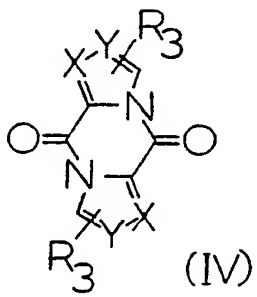
with an acid of formula



(III)

or a reactive derivative thereof, wherein A, R_1, R_2, R_3 and R_4 are as defined above.

As reactive derivatives of the acid of formula III wherein R_4 is lower alkyl mention is made of the acid halide, e.g. chloride or an anhydride which derivatives give corresponding compounds of formula I wherein R_4 is lower alkyl. Acids of formula III may also be coupled to the amine of formula II by using a coupling reagent such as those well known in the art of peptide chemistry, in particular a carbodiimide e.g. dicyclohexylcarbodiimide. Other reactive derivatives of the acids of formula III include ester derivatives e.g. methyl, phenyl or substituted phenyl esters such as nitro- or halo-substituted phenyl esters. Further derivatives include compounds of formula (IV) in which one of X or Y is N and the other is CH

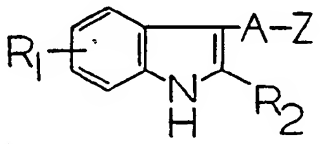


(IV)

wherein R_3 is as defined above, which compounds give corresponding compounds of formula I wherein R_4 is hydrogen.

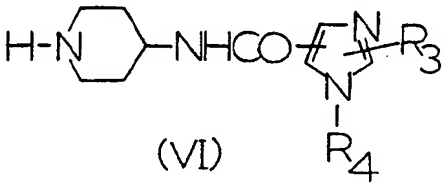
Compounds of formula IV are prepared by reacting the corresponding imidazole methyl ester with a thionyl halide, e.g. $SOCl_2$.

In a second general process compounds of formula I may be prepared by reacting a compound of formula



(V)

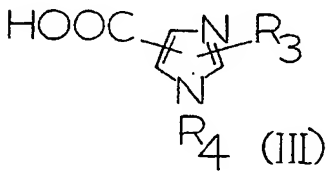
with a compound of general formula:



(VI)

in which formulae A, R_1, R_2, R_3, R_4 are as defined above and Z is a halogen atom or an equivalent replaceable radical, e.g. an organic sulphonyl radical such as tosyl. Examples of Z are chlorine, bromine. Alternatively Y can represent OH in which case the reaction may be effected using a catalyst, e.g. Raney nickel according to the procedure set forth in UK Patent Specification No. 1,375,836.

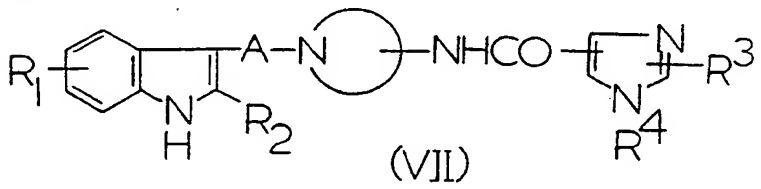
The starting materials of general formula V are known compounds or can be made following the methods known for preparing compounds of this type, e.g. by reducing the corresponding carboxyl compounds followed by halogenation. The starting material of general formula VI can be prepared by forming the oxime of a N-benzyl-4-piperidone, reducing to give the amine, acylating with an acid of general formula



(III)

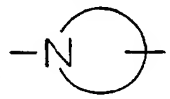
or a reactive derivative thereof, as described above in connection with the first process, and then hydrogenolysing to replace the N-benzyl group by N–H.

In a third process compounds of formula I may be prepared by reducing compounds of formula

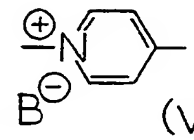


(VII)

wherein

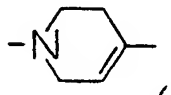


is a ring system of formula



(VIIa)

or



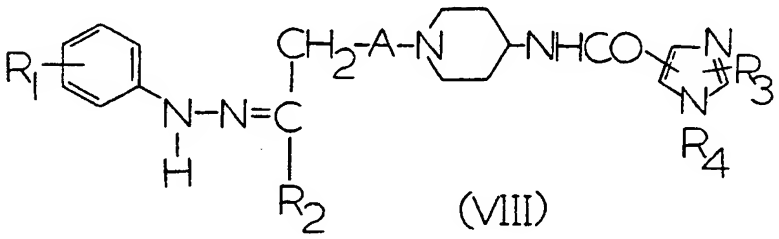
(VIIb)

A and R_{1-4} are as defined above and $B^{\ominus}$ is an anion. Methods for carrying out this reduction are extensively described in our UK Patent Specifications Nos. 1218570 and 1542137. For example reduction of either ring system VIIa or VIIb may be carried out using an alkali metal borohydride in a secondary alkanol solvent having 3–5 carbon atoms, e.g. isopropanol. Alternatively reduction may be effected by catalytic hydrogenation, e.g. using palladium on charcoal.

Starting materials of formula VII having a ring system VIIa may be prepared by acylating a 4-aminopyridine with an acid of formula III, or a reactive derivative thereof, and reacting the product with a compound of formula V in the manner described for the first process. Compounds of formula VII having a ring system of formula VIIb can be prepared by reducing a corresponding compound of formula VII having a ring system VIIa using an alkali metal borohydride in methanol solvent. In any of the aforementioned reductions, when A is oxoalkylene, such groups may also be reduced to alkylene or hydroxy-alkylene or if desired may be protected by methods known in the art, e.g. by forming a ketal.

Accordingly this invention also provides a further process for preparing compounds of formula I wherein A is lower alkylene or hydroxyalkylene which comprises reducing a compound of formula I wherein A is oxoalkylene.

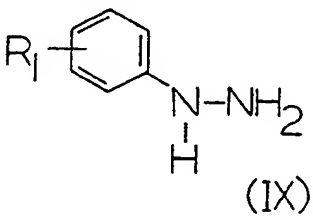
Yet a further process for preparing compounds of formula I comprises carrying out a Fischer indole synthesis on a compound of general formula



(VIII)

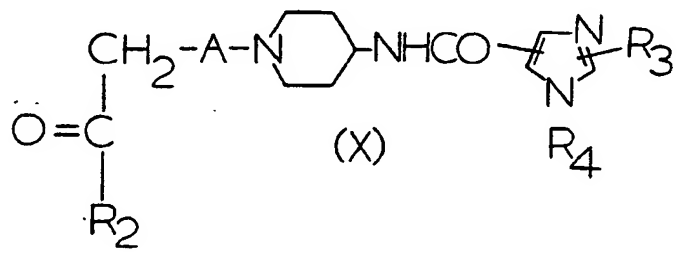
wherein R_1, R_2, R_3, R_4 and A are as defined herein above.

The starting material can be prepared by condensing a phenyl hydrazine of formula



(IX)

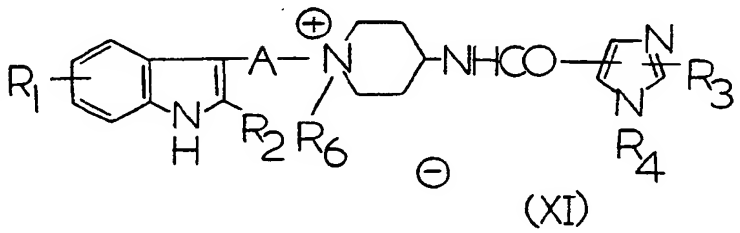
with an aldehyde or ketone of general formula



(X)

in which formulae R_1, R_2, R_3, R_4 and A are as defined above.

A still further process for preparing a compound of formula I comprises treating a compound of formula XI



(XI)

wherein R_{1-4}, are as defined above, R_6 is an organic quaternizing group which can be removed under mild conditions, e.g. hydrogenolysis, and $B^{\ominus}$ is an anion, under mild conditions effective to remove the group R_6. For a description of this process and methods for making compounds of formula XI see UK Patent Specification No. 1,399,608.

Compounds of formula I wherein A is an alkylene chain may be prepared from corresponding compounds of formula I wherein A is $-CO(CH_2)_n-$ by reduction according to the process described in UK Patent Specification No. 1,543,619 using an alkali meal borohydride in a solvent such as alkanols of 2 to 4 atoms, glycol ethers or dioxane.

The reactions outlined above usually are carried out in a solvent which is inert under the reaction conditions, for example an alcohol such as methanol, ethanol or propan-2-ol, ether, dioxane, dimethylformamide, pyridine, water, dimethoxy-ethane, methylene chloride, tetrahydrofuran and acetic acid or mixtures of such solvents. The most suitable solvent system is chosen and varies depending on the particular reactants being employed. If necessary heating the reactants in solution under reflux can be carried out, and if necessary heating under high pressures may also be used.

If necessary, in any of the reactions hereinbefore described, reactive substituent groups may be blocked during a reaction and released at a later stage. As already indicated the novel compounds provided by the invention contain a basic nitrogen atom and thus can form acid addition salts with acids (particularly pharmaceutically acceptable acids) or quaternary ammonium salts, for example with alkyl halides or aralkyl halides (particularly methyl iodide or benzyl chloride or bromide). The acid addition salts may either be formed *in situ* during the hereinbefore described processes and isolated therefrom or a free base may be treated with the appropriate acid in the presence of a suitable solvent and then the salt isolated. The quaternary salts may be prepared by treating the free base with the appropriate halide in the presence or absence of a solvent.

Examples of acid addition salts are those formed from inorganic and organic acids, such as sulphuric, hydrochloric, hydrobromic, phosphoric, tartaric, fumaric, maleic, citric, acetic, formic, methanesulphonic and p-toluenesulphonic acids.

The invention provides a pharmaceutical composition comprising a compound of formula I or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable carrier. Any suitable carrier known in the art can be used to prepare the pharmaceutical compositions. In such a composition, the carrier may be a solid, liquid or mixture of a solid and a liquid. Solid form compositions include powders, tablets and capsules. A solid carrier can be one or more substances which may also act as flavouring agents, lubricants, solubilisers, suspending agents, binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets the active ingredient is mixed with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from 5 to 99%, preferably 10–80% of the active ingredient. Suitable solid

carriers are magnesium carbonate, magnesium stearate, talc, lactose, pectin, dextrin starch, gelatin, tragacanth, methylcellulose, sodium carboxymethyl cellulose, a low melting wax and cocoa butter. The term "composition" is intended to include the formulation of an active ingredient with encapsulating material as carrier to give a capsule in which the active ingredient (with or without other carriers) is surrounded by the carrier, which is thus in association with it. Similarly cachets are included. Sterile liquid form compositions include sterile solutions, suspensions, emulsions, syrups and elixirs. The active ingredients can be dissolved or suspended in a pharmaceutically acceptable sterile liquid carrier, such as sterile water, sterile organic solvent or a mixture of both. Preferably a liquid carrier is one suitable for parenteral injection. Where the active ingredient is sufficiently soluble it can be dissolved in normal saline as a carrier; if it is too insoluble for this it can often be dissolved in suitable organic solvent, for instance aqueous propylene glycol or polyethylene glycol solutions. Aqueous propylene glycol containing from 10 to 75% of the glycol by weight is generally suitable. In other instances other compositions can be made by dispersing the finely-divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution, or in a suitable oil, for instance arachis oil. Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by intramuscular, intraperitoneal or subcutaneous injection. In many instances a compound is orally active and can be administered orally either in liquid or solid composition form.

Preferably the pharmaceutical composition is in unit dosage form, e.g. as tablets or capsules. In such form, the composition is sub-divided in unit doses containing appropriate quantities of the active ingredients; the unit dosage forms can be packaged compositions, for example packeted powders or vials or ampoules. The unit dosage form can be a capsule, cachet or tablet itself, or it can be the appropriate number of any of these in package form. The quantity of the active ingredient in a unit dose of composition may be varied or adjusted from 5 mg, or less to 500 mg. or more, according to the particular need and the activity of the active ingredient. The invention also includes the compounds in the absence of the carrier where the compounds are in unit dosage form.

The following Examples 1–4 illustrate the invention: Example 5 illustrates the preparation of a starting material.

EXAMPLE 1

N-[1-(2[1H-indol-3-yl]ethyl)piperidin-4-yl]-1-methyl-1H-imidazole-2-carboxamide

A melt of 3-[2-(4-amino-1-piperidyl)ethyl]indole (1.0g, 4.11mmol), 2-hydroxypyridine (0.3g, 3.16mmol) and 2-methoxycarbonyl-1-methyl-1*H*-imidazole (0.57g, 4.07mmol) was heated at 160°C for 3 hours under N_2. More 2-methoxycarbonyl-1-methyl-1H-imidazole (5 drops) was added and heating continued for a further $1\frac{1}{2}$ hours. The mixture was cooled and chromatographed on silica (100–200 aktiv) eluting with absolute ethanol. The title compound was isolated as a brown glass (0.97g,).

This was dissolved in hot ethanol (ca. 10cm^3) and ethanolic HCl added to give an acidic solution from which the dihydrochloride of the title compound crystallised on cooling in ice, 0.48g,m.p. 250–53°C (on heating from cold sample gums 140–160°C, crystallises 225–40°, starts to decompose at 245° then melts as above).

Analysis: Found: C, 56.60; H, 6.23; N, 16.86%
$C_{20}H_{25}N_5O.2HCl$ requires: c, 56.61; H, 6.41; N, 16.50%.

EXAMPLE 2

N-[1-(2-[1H-indol-3-yl]ethyl)4-piperidinyl]-1H-imidazole-2-carboxamide

a) Diimidazo[1,2-*a*:1'2'-*d*]tetrahydropyrazine-4,8-dione dihydrochloride (0.32g, 1.23 mmol) was added to a suspension of 3-[2-(4-amino-1-piperidyl)ethyl]indole (0.59g, 2.43 mmol) and triethylamine (0.3g, 2.97 mmol) in dry pyridine (3cm^3). A brown solution was formed which soon crystallised to give a solid mass. After leaving at room temperature for 3 hours the mixture was diluted with water (6cm^3) and the solid collected, washed with water and dried. A second crop was obtained by further dilution of the filtrate, which was combined with the first to give 0.74g.

The sample was suspended in boiling ethanol (8 cm^3) and ethanolic HCl added to give an acidic solution which was cooled in ice to deposit a gum. This was induced to crystallise by squashing vigorously with a spatula; it was collected, washed with ethanol then ether and dried to give 0.86g of the title compound as the dihydrochloride hemiethanolate mp. 221–3°C (gums above 200°C).

Analysis:
Found: C, 55.63; H, 6.64; N, 15.80%
$C_{19}H_{23}N_5O.2HCl.\frac{1}{2}C_2H_5OH$ requires: C, 55.43; H, 6.51; N, 16.16%.

EXAMPLE 3

N-[(1-(2-[1H-Indol-3-yl]ethyl)piperidin-4-yl]1H-imidazole-4-carboxamide

A mixture of 3-[2-(4-amino-1-piperidyl)ethyl]indole (1.2g, 5 mmol), acetonitrile (10 cm^3), and diimidazo-[1,5-*a*:1',5-*d*] tetrahydropyrazine-4,8-dione (0.5g, excess) was heated at reflux for 0.75 hours. The solvent was evaporated and the solid eluted down a silica column (40g, Woelm Act I) with chloroform/methanol/triethylamine, initially (90:10:0.1 by volume) and finally (75:25:0.1 by volume) to give 0.75g of product. The base was dissolved in ethanol (8 cm^3) and acidified with ethanol HCl, on refrigeration overnight the crystalline title compound was collected 0.8g as the dihydrochloride salt. Recrystallisation from methanol gave 0.4g of pure material m.p. 247–50°C.

Analysis

Found: C, 55.81; H,5.99; N, 17.07%

$C_{19}H_{23}N_5 0.2HCl$ requires C, 55.61; H, 6.14; N, 17.07%.

EXAMPLE 4

N-[1-(2-[1H-Indol-3-yl]ethyl)piperid-4-yl]-5-methyl-1H-imidazole-4-carboxamide

Dicyclohexylcarbodiimide (1.24g, 6mmol) was added to a stirred solution of 3-[2-(4-amino-1-piperidyl)ethyl]-indole (1.2g, 5mmol) and 5-methylimidazole-4-carboxylic acid hydrochloride (0.89g, 5.5mmol) in pyridine (10cm^3).

A gum precipitated immediately and prevented further stirring. The mixture was allowed to stand 0.5hours then briefly heated to reflux during which a fine crystalline precipitate formed. The solvent was then evaporated and the residue triturated with hydrochloric acid (2M, 30cm^3 and 10cm^3) and filtered. The filtrate was basified with ammonia to precipitate a brown gum which was collected and washed by decantation. The gum was eluted down a column of silica (30g) using $CHCl_3$/MeOH/Et_3N, initially in the ratio 95:5:0.1 by volume but increasing stepwise to 75:20:0.1 by volume, to give 1g of the title compound as a foam. This was dissolved in ethanol (10cm^3) and acidified with ethanolic hydrogen chloride to give the dihydrochloride salt 0.76g, mp 215–217°C.

Analysis

Found C, 57.00; H, 6.88; N, 16.60%

$C_{20}H_{25}N_5 0.2HCl$ requires C, 56.60; H, 6.41; N, 16.50%.

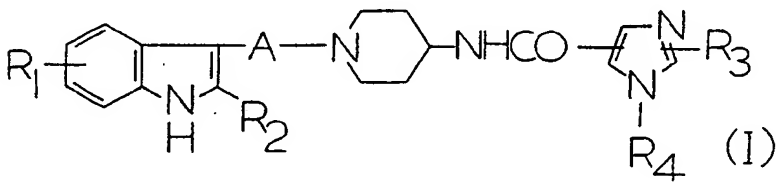
EXAMPLE 5

Preparation of diimidazo[1,2-a:1',2-d]tetrahydropyrazine-4, 8-dione

A suspension of imidazole-2-carboxylic acid (0.71g, 6.34 mmol dry, 5.46mmol monohydrate) in thionyl chloride (6.5 ml) was heated to boiling. Evolution of gas was seen at 60°. Heating was continued for 2 hours to give a pale yellow suspension which was cooled then poured into toluene (23 ml). The solid was collected and washed with ether to give a pale yellow solid 0.60g. (Dried at 60°C *in vacuo*) mop 173–6°C (dec).

CLAIMS

1. A compound of formula



(I)

wherein R_1 is hydrogen, lower alkyl, halogen, lower alkoxy or hydroxy,
R_2, R_3 and R_4 independently represent hydrogen or lower alkyl,
A represents an alkylene, oxoalkylene or hydroxy-alkylene chain each having 2 to 6 carbon atoms or a pharmaceutically acceptable salt thereof.

2. A compound as claimed in Claim 1 wherein A is a chain of formula $-(CH_2)_n$, $CO(CH_2)_{n-1}$ or $-CHOH(CH_2)_{n-1}$ wherein n is an integer from 2 to 4, or A is $-CH_2CH(CH_3)-$, $-COCH(CH_3)-$ or $-CHOH.CH(CH_3)-$

3. A compound as claimed in Claim 2 wherein n is 2.

4. A compound as claimed in any one of Claims 1 to 3 wherein any of R_1–R_4 when alkyl is methyl, ethyl, n-propyl or isopropyl.

5. A compound as claimed in any one of Claims 1 to 4 wherein the imidazolyl group is bonded via the 2 or 4 position.

6. N-[1-(2-[1*H*-indol-3-yl]ethyl)piperidin-4-yl]-1-methyl-1*H*-imidazole-2-carboxamide or a pharma-

ceutically acceptable salt thereof.

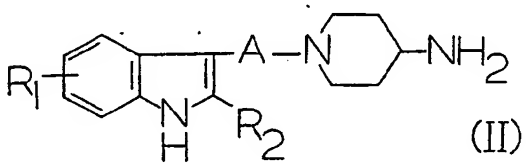
7. N-[1-(2-[1*H*-indol-3-yl]ethyl)piperidin-4-yl]-1*H*-imidazole-2-carboxamide or a pharmaceutically acceptable salt thereof.

8. N-[1-(2-[1*H*-Indol-3-yl]ethyl)piperidin-4-yl]-imidazole-4-carboxamide or a pharmaceutically acceptable salt thereof.

9. N-[1-(2-[1H-Indol-3-yl]ethyl)piperid-4-yl]-5-methylimidazole-4-carboxamide or a pharmaceutically acceptable salt thereof.

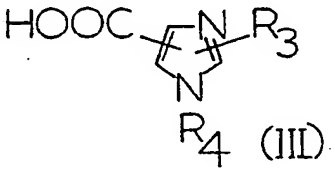
10. A compound as claimed in any one of Claims 1 to 9 which is in the form of a salt from an acid selected from sulphuric, hydrochloric, hydrobromic, phosphoric, tartaric, fumaric, maleic, citric, acetic, formic, methanesulphonic and p-toluene-sulphonic acid.

11. A process for preparing a compound of formula I as defined in Claim 1 or a pharmaceutically acceptable salt thereof which comprises acylating a compound of formula



(II)

with an acid of formula



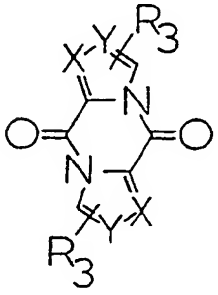
(III)

or a reactive derivative thereof, wherein A, R_1, R_2, R_3 and R_4 are as defined in Claim 1, if desired converting the product to a salt thereof.

12. A process as claimed in Claim 11 in which R_4 is lower alkyl and the reactive derivative of the acid of formula III is the acid halide or an anhydride.

13. A process as claimed in Claim 11 in which an acid of formula III is used in the presence of a coupling reagent.

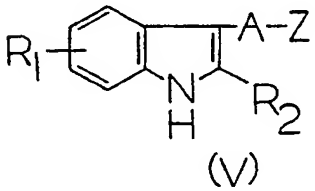
14. A process as claimed in Claim 11 in which the reactive derivative of the acid is an ester or a compound of formula



in which one of X and Y is N the other is CH and R_3 is as defined in Claim 1.

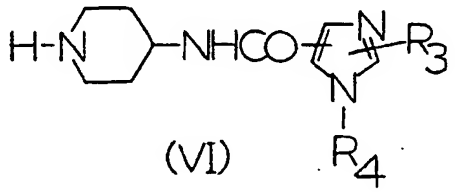
15. A process for preparing a compound of formula I as defined in Claim 1 which comprises

a) reacting a compound of formula



(V)

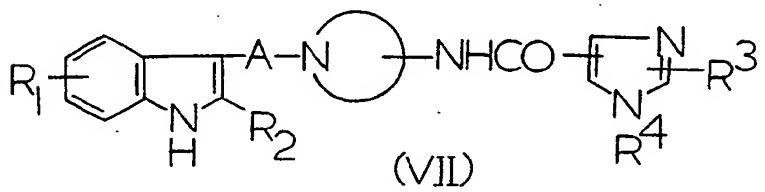
with a compound of general formula:



(VI)

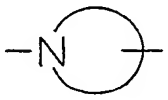
in which formulae A, R_1, R_2, R_3, R_4 are as defined in Claim 1 and Y is a halogen atom or an equivalent replaceable radical,

b) reducing a compound of formula

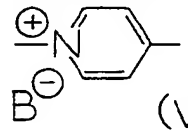


(VII)

wherein

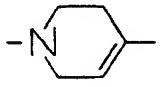


is a ring system of formula



(VIIa)

or

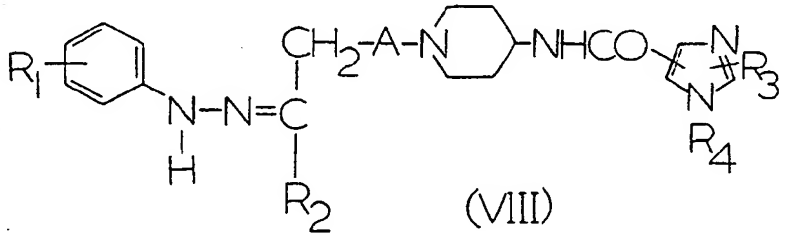


(VIIb)

A and R_{1-4} are as defined in Claim 1 and $B^{\ominus}$ is an anion,

or c) reducing a compound of formula I wherein A is oxoalkylene of 2 to 6 carbon atoms to give a compound of formula I wherein A is lower alkylene or hydroxyalkylene

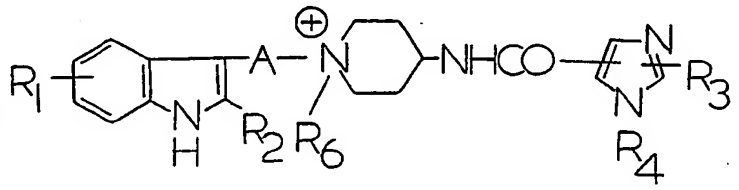
or d) carrying out a Fischer indole synthesis on a compound of general formula



(VIII)

wherein R, R_1, R_2, R_3, R_4 and A are as defined in Claim 1

or e) treating a compound of formula XI



(XI)

wherein R_{1-4}, are as defined in Claim 1, R_6 is an organic quaternizing group which can be removed under mild conditions and $B^{\ominus}$ is an anion, under mild conditions effective to remove the group R_6

or f) acidifying or quaternizing a basic compound of formula I as defined in Claim 1 to form an acid addition or quaternary ammonium salt.

16. A process for preparing a compound of formula I as defined in Claim 1 substantially as hereinbefore described with reference to any one of Examples 1 to 4.

17. A compound of formula I whenever prepared by a process as claimed in any one of Claims 11 to 16.

18. A pharmaceutical composition comprising a compound of formula I as claimed in any one of Claims 1 to 10 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

19. A pharmaceutical carrier as claimed in Claim 18 when in unit dosage form.

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